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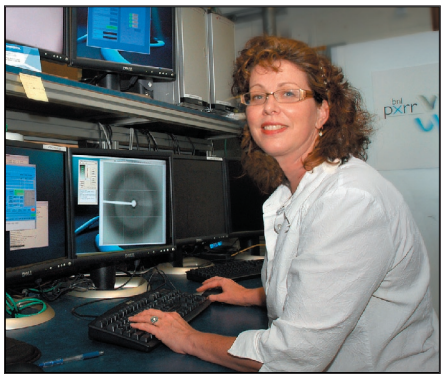
Featured Highlights
from the National Synchrotron Light Source

Potent Peptides Inhibit HIV Entry Into Cells

Protein analysis at Brookhaven's light source helps researchers in design of new AIDS drugs

Based in part on protein structures determined at the NSLS, scientists at the University of Utah have developed new peptides that appear to be significantly more effective at blocking HIV's entry into cells than other drugs in their class. In a paper published online by the *Proceedings of the National Academy of Sciences* the week of October 8, 2007, the researchers say these peptides are sufficiently potent to begin pre-clinical studies as a new class of agents for the prevention and treatment of HIV/AIDS.

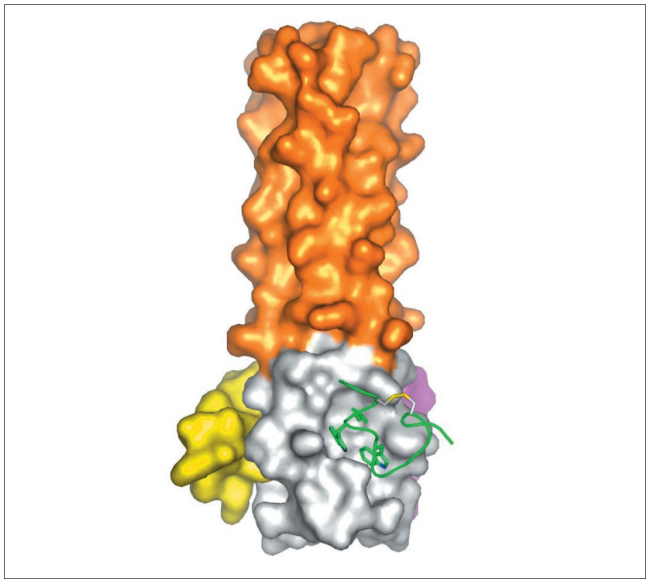


Annie Heroux

"Our 'D-peptides' offer several potential therapeutic advantages over existing peptide entry inhibitors, which are costly, require high dose injections, and suffer from the emergence of drug-resistance," said University of Utah biochemist Michael S. Kay, lead author on the paper. "In contrast, our D-peptides resist degradation, so they have the potential to be administered by mouth and last longer in the bloodstream. Since these inhibitors have a unique inhibitory mechanism, they should work well in combination with existing HIV inhibitors."

The researchers were particularly interested in developing drugs to bind to an essential "pocket" structure found in all HIV strains that was previously identified as a promising drug target using structures determined at Brookhaven's NSLS. Numerous previous attempts to target this pocket failed to produce potent and non-toxic pocket-specific entry inhibitors. In the current work, the researchers used a high-throughput technique to screen a "library" containing hundreds of millions of peptides to identify the rare peptides that would bind to the pocket structure and inhibit HIV entry.

After identifying the most promising candidate peptides, the researchers analyzed the structure of these peptides bound to the target protein using x-ray crystallography at NSLS beamline X29. In this technique,



Structure of D-peptide inhibitors (green, yellow, and purple) bound to an HIV protein mimic in three "pockets" that are essential to the virus ability to enter cells. Blocking the pockets thwarts entry and reduces infectivity.

researchers analyze how an extremely bright beam of x-rays, available only at synchrotron sources, bounces off and is refracted by the sample to determine the positions of individual atoms.

"These structures reveal details of how the peptides bind and guide the development of future inhibitors," said paper co-author Annie Heroux, a biologist and crystallography specialist at Brookhaven Lab.

This structure-assisted design led to the discovery of D-peptides with up to a 40,000-fold improved antiviral potency over previously reported D-peptides. The structures also suggest ways to engineer the peptides to reduce the chance of drug resistance.

This research was funded by the National Institutes of Health, the University of Utah Technology Commercialization Project, and by the American Cancer Society. Operational funding for the NSLS is provided by the Office of Basic Energy Sciences within the U.S. Department of Energy's Office of Science and by the National Institutes of Health.

—Karen McNulty Walsh